Rejections under 35 U.S.C. § 103 (Pages 2-7, paragraphs 2-4 of the Office Action)

Huse '726 in view of Gelfand '292 (Paragraph 3 of the Office Action)

The Examiner rejects claims 20-25, 27-29 and 31-41 under 35 U.S.C. § 103(a) for allegedly being obvious over Huse '762 (USP 5,681,726) in view of Gelfand '292 (USP 5,939,292). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Huse '726 discloses a method for amplifying a DNA fragment containing a nucleotide analog via PCR. Huse '726 fails to disclose a method for amplifying DNA in the presence of two or more kinds of nucleotide analogs that do not cause termination of the DNA amplification, wherein there is a uniform incorporation of these nucleotide analogs into a targeted nucleic acid during amplification. The Examiner attempts to make up for the deficiencies of Huse '726 by combining therewith the disclosure of Gelfand '292.

The Examiner asserts that "Gelfand et al teach the method for amplifying a DNA in the presence of two or more kinds of nucleotide analogs, wherein the nucleotide analogs are uniformly incorporated into the resulting DNA, thereby selectively

amplifying DNA of a target sequence (Examples I-X)." Applicants respectfully disagree.

Gelfand '292 actually discloses modified thermostable DNA polymerases which have enhanced efficiency for incorporating *unconventional nucleotides*, such as ribonucleotide, into DNA product, and DNA sequencing using the modified thermostable DNA polymerases. See column 1, lines 1-8, in the section entitled "Field of the Invention," and the like in Gelfand '292.

As defined on column 4, lines 36-40, "dNTP" includes c7dGTP and dITP, which is used in the present invention. However, the term "unconventional (nucleotides)" means, as described in column 6, lines 1-7, those nucleotides which are modified at the 2' position of the ribose sugar in comparison with conventional dNTPs. Therefore, the "nucleotide analog" of the present invention is completely different from the "unconventional nucleotide" of Gelfand '292.

Accordingly, Gelfand '292 discloses a method in which the need for chain-terminating ddNTPs is eliminated. See column 3, lines 16-17. As such, the disclosed method is carried out on the presumption that a ribonucleotide is used.

Furthermore, as to Examples I-X of Gelfand '292 referred to by the Examiner, Applicants point out that Examples I, VII and

VIII each show preparation and expression of a modified DNA polymerase with enhanced efficiency for incorporating rNTP; that Examples III and V each show an experiment using **one kind of 3' deoxy derivative having a property of terminating DNA extension** (for instance, column 21, line 10, column 22, line 48); and that Examples II, IV, VI, IX and X each show an experiment using one kind of a ribonucleotide. **Therefore, all of the examples show reactions in the presence of a single kind of nucleotide in one reaction mixture.** Since none of these examples are reactions in the presence of at least two nucleotides, all of the claimed elements of the present invention are not met.

Incidentally, in the table in Example II, the table may mistakenly be understood to show the results of a reaction in the copresence of rCTP, rGTP and rUTP. However, as described on column 19, line 65 to column 20, line 5, rCTP, rGTP and rUTP are each used in a different reaction system. The same can be said for the table in Example IX. Thus, none of the reactions are in the presence of at least two nucleotides.

The Examiner asserts that Gelfand '292 discloses uniform incorporation of nucleotide analogs. Applicants respectfully disagree. The DNA polymerase disclosed by Gelfand '292 possesses "reduced discrimination against incorporation of an

unconventional nucleotide in comparison to said naturally occurring thermostable DNA polymerase." However, this "reduced discrimination" is not equivalent to the instantly claimed uniform incorporation of nucleotide analogs. As is disclosed in column 14, lines 19-35, a ratio of the amount of dNTP incorporated into DNA to the amount of rNTP incorporated into DNA is lowered as compared to a conventional DNA polymerase. Therefore, the term "reduced discrimination" is intended to mean easiness of incorporation of rNTP into DNA, rather than "uniformity of incorporation." Therefore, Gelfand '292 merely discloses an efficient incorporation of rNTP in DNA products, and does not disclose or suggest the uniform incorporation of rNTP.

Finally, the Applicants point out that Huse '762 is concerned with cDNA cloning in which a primer/linker and a restriction enzyme digestion are combined in addition to the nucleotide analog. These teachings are not relevant to those of Gelfand '292 which discloses a modified DNA polymerase which has enhanced incorporation efficiency of rNTP into DNA, DNA nucleotide sequencing and the preparation of labeled DNA fragment. Therefore, one of ordinary skill in the art would not be motivated to combine Huse '762 with Gelfand '292.

Further, even if the nucleotide analog used in Huse '762 were used in the method disclosed in Gelfand '292, an ordinary DNA sequencing would merely be carried out. Also, although it is possible to use the DNA polymerase of Gelfand '292 in the DNA synthesis disclosed in Huse '762, in such a case it would be sufficient to use only a single nucleotide analog.

For these reasons, the rejection is improper and should be withdrawn.

Rejection over Huse '726 in view of Gelfand '292 and further in view of Dodge '117 (Paragraph 4 of the Office Action)

The Examiner rejects claims 26 and 30 under 35 U.S.C. § 103(a) for allegedly being obvious over Huse '762 in view of Gelfand '292, and further in view of Dodge '117 (USP 5,912,117). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner relies on Dodge '117 to teach a compound for lowering Tm value. However, the hypothetical combination of these references still does not make the present invention obvious since none of the references disclose amplification in the presence of two or more nucleotide analogs, wherein the

nucleotide analogs do not cause termination of the amplification.

For the above reasons, the rejection under 35 U.S.C. § 103 is improper and should be formally withdrawn.

Conclusion

In summary, all of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action on the merits of the present application is thereby requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any

additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly, extension of time fees.

Respectfully submitted,

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